GeneStrat® Genomic Test Executive Summary

In 2019, more than 1.7 million people in the US are expected to be diagnosed with cancer.[1] Of those new cases, lung cancer is the third most common diagnosis and is the leading cause of cancer death. About 20-30% of US patients diagnosed with non-small cell lung cancer (NSCLC) are found to be positive for driver mutations. For these patients, targeted therapies are readily available and proven to be effective in multiple clinical trials. Currently national guidelines including ASCO, CAP, IASLC, AMP and NCCN recommend mutation testing be done at diagnosis to guide therapy choice. The standard approach for identification of actionable variants in patients with NSCLC is through the analysis of a tissue biopsy. However, 25% of patients are not candidates for invasive biopsies and many more will not have sufficient tissue for all necessary mutation testing following the initial diagnostic workup. Further, 80% of lung cancer patients will not have their tissue-based genomic test results available for the initial oncology consult..[2] As a result, 1 in 4 patients will begin treatment prior to receiving their mutation results, which can lead to poorer outcomes, increased patient anxiety, and decreased overall response to therapy.[3,4] These factors hinder a physician's ability to select an optimal treatment strategy for patients.

The GeneStrat® genomic test is a highly accurate, clinically validated blood-based mutation analysis that offers actionable, genetic information for patients with advanced NSCLC. With a simple blood draw, the GeneStrat test identifies whether a patient has a driver mutation in order to assist physicians in prescribing targeted therapies in a timely manner and without the need for a tissue biopsy. Based on the ordering physician and specific patient's needs, GeneStrat can test for Epidermal Growth Factor Receptor (*EGFR)*, Kirsten rat sarcoma oncogene homolog (*KRAS)* and B-Raf (*BRAF)* mutations, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK), Proto-oncogene tyrosine-protein kinase (ROS-1), and rearranged during transfection mutation (RET) fusions. Understanding whether anomalies in these genes are present allows oncologists to consider use of targeted therapies for their patients. GeneStrat offers reliable detection of guideline-recommended mutations, provides results within 72 hours of sample shipment to the Biodesix laboratory, and is 97% concordant to tissue-based mutation testing.[5]

Currently, physicians utilize tissue-based testing to obtain genomic information to guide therapy as recommended by ASCO, CAP, IASLC, AMP and NCCN Guidelines. These same guidelines, however, and specifically NCCN, recognize the limitations associated with tissue-based testing and discuss the advantages of liquid biopsy (blood-based testing) options. To supplement these guidelines, below a Executive Summary including a Population, Intervention, Comparators, and Outcomes (PICO) assessment performed for GeneStrat as a recommended blood-based testing at time of diagnosis for patients with advanced NSCLC:

Population: Individuals with newly diagnosed, advanced stage (stages IIIb and IV) non-small cell lung cancer.

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[1] https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf

[2] Lim C, Tsao MS, Le LW, et al. Biomarker testing and time to treatment decision in patients with advanced non-small-cell lung cancer. Annals of Oncology (2015): mdv208. PMID 25922063

[3] Samson, P., Patel, A., Garrett, T., Crabtree, T., Kreisel, D., Krupnick, A. S., & Puri, V. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. The Annals of thoracic surgery, 2015; 99(6), 1906-1913. PMID 25890663

[4] Lo, Dorothy, Zeldin, Robert, Skrastins, Roland, Fraser, Ian, et al. Time to Treat: A System Redesign Focusing on Decreasing the Time from Suspicion of Lung Cancer to Diagnosis. Journal of Thoracic Oncology; 2007; 2(11) 1001-1006. PMID 17975490

[5] Mellert H, Foreman T, Jackson L, et al. Development and Clinical Utility of a Blood-based Test Service for the Rapid Identification of Actionable Mutations in NSCLC. Journal of Molecular Diagnostics May 2017.

- All clinical trials and studies included in this PICO overview are performed on patients with advanced stage NSCLC. Though currently being evaluated on early stage patients, the greatest clinical utility and guideline recommendations for blood-based genomic testing is for advanced stage NSCLC patients.

Intervention: Blood-based, rapid turnaround, genomic testing may be used to measure clinically actionable mutations and initiate targeted treatment or clinical trial enrollment within 72 hours of diagnosis.

- It has been demonstrated that due to limitations with tissue biopsies including invasiveness of the biopsy and lack of sufficient tissue, up to 30% of patients at a community-based academic center did not undergo guideline-recommended molecular testing, despite an institutional reflex testing policy for tissue.[6]
- Time to treatment has been found to be the shortest when patients had blood-based genomic results at their first oncology appointment (most often when ordered by the pulmonologist)[7]
- Utilizing a blood-based reflex strategy including genomic and proteomic testing earlier at time of diagnosis may help patients receive appropriate treatment faster, therefore potentially improve overall survival in patients with NSCLC.[8]

Comparators: Comparators to GeneStrat include traditional tissue-based mutation testing as well as other on-market liquid biopsy tests including the Oncotype SEQ test, the Biocept Target Selector Test, Foundation Medicine's Foundation ACT test, Guardant365 Next Gene Sequencing (NGS) test, and other liquid-based NGS tests.

In studies comparing tissue-based genomic testing with blood-based testing:

- Blood-based testing decreased time from diagnosis to treatment by making molecular profile status available earlier and reducing wait times due to re-biopsies.[9]
- The observed turn-around time from blood-based (GeneStrat) testing to results was an average of 1.4 days (33 hours) v. 12 days for tissue-based testing. All patients had results available prior to their next physician consultation and all patients initiated treatment within 7 days of the blood draw. The study concluded that ordering the GeneStrat test for the purpose of biomarker testing would result in faster time to test results and faster time to treatment than tissue-based testing.[10]
- By using a robust ddPCR methodology and a minimal amount of blood, the GeneStrat test, with 72 hour turnaround time to results and comprehensive clinical validation[11], remains the best blood-based targeted mutation testing option on the market.

Outcomes: The ability to have fast, accurate, and tailored mutation information at time of diagnosis has been proven to improve time to treatment, directly impacting patient quality of life (QOL) and overall survival (OS).

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[6] Inal, C., Yilmaz, E., Cheng, H., Zhu, C., Pullman, J., Gucalp, R. A., & Piperdi, B. (2014, May). I4. In ASCO Annual Meeting Proceedings (Vol. 32, No. 15_suppl, p. 8098)

[7] Magee, M et al. Costs and Outcomes Comparisons of Tissue and Blood Based Biopsies for the Purpose of Biomarker Testing for advanced Non-Small Cell Lung Cancer. Presented at ISPOR, Washington DC, March 2016.

[8] Bowling, M et al. Shortening time from Diagnosis to Treatment in NSCLC: Are Blood-based Biopsies the Answer? Presented at IASLC, Chicago 2016 Abstract 143, Program PS01.16

[9] Magee, M et al. Costs and Outcomes Comparisons of Tissue and Blood Based Biopsies for the Purpose of Biomarker Testing for advanced Non-Small Cell Lung Cancer. Presented at ISPOR, Washington DC, March 2016.

[10] Bowling, M et al. Shortening time from Diagnosis to Treatment in NSCLC: Are Blood-based Biopsies the Answer? Presented at IASLC, Chicago 2016 Abstract 143, Program PS01.16

[11] Mellert H, Foreman T, Jackson L, et al. Development and Clinical Utility of a Blood-based Test Service for the Rapid Identification of Actionable Mutations in NSCLC. Journal of Molecular Diagnostics May 2017.

- **Improvement in QOL:** Investigators have shown that when compared to CT guided needle biopsy, a blood-based genomic test requiring a blood draw had no adverse events. CT guided needle biopsy had the highest rate of complications with 15% of patients presenting some form of pneumothorax or lung collapse, and a small minority of patients suffered from hemorrhage and respiratory distress following the biopsy procedure. Complications resulted in hospitalization for 8.27% of patients.[12]
- **Improvement in OS:** Identifying genomic mutations prior to initiating treatment has been proven to improve OS for patients harboring a mutation. One example includes findings from the OPTIMAL trial which showed that patients who received sequential combination of EGFR-TKI and chemotherapy had significantly improved OS compared with patients who received EGFR-TKI or chemotherapy alone. This improvement in OS can only be achieved when patients have the ability to receive their mutation information at in a timely manner upon diagnosis, prior to initiating treatment.[13]
- **Improvement in OS:** Accounting for tumor heterogeneity using blood-based genomic testing has been proven to improve OS for patients by ensuring that mutations are identified and optimal treatments are administered. Most often, heterogeneity of a tumor cannot be accounted for by tissue biopsy and therefore mutations are missed, resulting in suboptimal treatments and negative impacts to patient survival.[14] 72 hour blood-based testing provides a comprehensive picture of the patient's tumor and allows for faster, optimal treatment to be administered, directly impacting patient OS.[15]

[12] Magee, M et al. Costs and Outcomes Comparisons of Tissue and Blood Based Biopsies for the Purpose of Biomarker Testing for advanced Non-Small Cell Lung Cancer. Presented at ISPOR, Washington DC, March 2016.
[13] Zhou, C, Wu, Y.L., Chen, G et al. Final Overall Survival results from a randomized, phase III study of erlotinib versus Chemotherapy as first-line treatment of EGFR-mutation-positive advanced non-small cell lung cancer (OPTIMAL, CTONG-08020). Annals of Oncology 26: 1877-1883 July 2015. PMID 26141208
[14] Remon, J, Majem, M. EGFR mutation heterogeneity and mixed response to EGFR tyrosine kinase inhibitors of non small cell lung cancer: a clue to overcoming resistance. Transl Lung Cancer Res 2013;2(6):445-448.
[15] Siravegna and Bardelli. Genome Biology 2014, 15:449 http://genomebiology.com/2014/15/8/449